



HAL
open science

Does arbovirus emergence in humans require adaptation to domestic mosquitoes?

Louis Lambrechts

► **To cite this version:**

Louis Lambrechts. Does arbovirus emergence in humans require adaptation to domestic mosquitoes?. Current Opinion in Virology, 2023, 60, pp.101315. 10.1016/j.coviro.2023.101315 . pasteur-04610596

HAL Id: pasteur-04610596

<https://pasteur.hal.science/pasteur-04610596>

Submitted on 13 Jun 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Does arbovirus emergence in humans require adaptation to domestic mosquitoes?

Louis Lambrechts*

Institut Pasteur, Université Paris Cité, CNRS UMR2000, Insect-Virus Interactions Unit, Paris, France

*Correspondence to: louis.lambrechts@pasteur.fr

Abstract

In the last few decades, several mosquito-borne arboviruses of zoonotic origin have established large-scale epidemic transmission cycles in the human population. It is often considered that arbovirus emergence is driven by adaptive evolution, such as virus adaptation for transmission by ‘domestic’ mosquito vector species that live in close association with humans. Here, I argue that although arbovirus adaptation to domestic mosquito vectors has been observed for several emerging arboviruses, it was generally not directly responsible for their initial emergence. Secondary adaptation to domestic mosquitoes often amplified epidemic transmission, however this was more likely a consequence than a cause of arbovirus emergence. Considering that emerging arboviruses are generally ‘pre-adapted’ for transmission by domestic mosquito vectors may help to enhance preparedness towards future arbovirus emergence events.

Introduction

The COVID-19 pandemic and the current outbreak of monkeypox virus are just the two most recent examples of emerging infectious diseases caused by zoonotic viruses introduced into the human population. Because humans are new hosts for these viruses, emergence is often associated with viral adaptation to human cell receptors and/or human-to-human transmission. This was the case for Ebola virus, which increased its infectivity for human cells, while reducing tropism for bat cells, during the 2013-2016 epidemic in West Africa [1]. The repeated emergence of more transmissible SARS-CoV-2 variants also represents evidence of its ongoing adaptation to human hosts [2]. However, viral adaptation to humans often does not appear to be necessary for the initial host jump. For instance, efforts to identify early adaptive mutations associated with higher human-to-human transmissibility of SARS-CoV-2 failed to identify obvious candidates [3]. Evolutionary analyses suggest that both efficient human-to-human transmission and human cell receptor usage were already present in ancestral bat-associated SARS-CoV-2 lineages [4]. In fact, SARS-CoV-2-like strains circulating in cave bats of northern Laos already have the potential to infect humans [5]. Likewise, hemorrhagic fever-causing arteriviruses circulating in wild non-human primates do not require major adaptations to replicate in human cells [6].

Here, I retrospectively examine the emergence of several mosquito-borne viruses in the last few decades to assess the extent to which viral adaptation to a new mosquito vector species was required for successful emergence in humans. The emergence of arthropod-borne viruses (arboviruses) is typically initiated by a spillover event that allows a virus to switch from a wildlife (enzootic) transmission cycle to a human (epidemic) transmission cycle. In the enzootic cycle (also referred to as the sylvatic cycle), the arbovirus is transmitted by wildlife-biting mosquito species, whereas in the human transmission cycle it is transmitted by human-biting mosquito species. This emergence scenario has been well described for yellow fever, dengue, chikungunya, and Zika viruses [7-9]. Worldwide, the two main vectors of these arboviruses are *Aedes aegypti* and *Aedes albopictus*, two 'domestic' mosquito species that thrive in human-dominated environments [10]. In addition, mosquitoes in the *Culex pipiens* complex have been involved in the emergence of West Nile virus in North America [11,12]. The initial arbovirus spillover event can be facilitated by 'bridge vectors' that bite both wild animals and humans [11-14].

Nearly all arboviruses are RNA viruses with a high evolutionary potential owing to their high mutation frequency and fast replication rate. However, the obligate host alternation of arboviruses is predicted to result in a fitness trade-off, whereby optimal replication in one host

involves a fitness cost in the other host [15]. Accordingly, arbovirus emergence via a change in host range should be less frequent than that of single-host RNA viruses. This fitness trade-off hypothesis has been supported by some studies [16], but not others [15]. In fact, adaptive evolution is generally considered a main driver of mosquito-borne virus emergence [15,17,18]. Virus adaptation to alternative mosquito vector species has often been put forward as a major factor underlying the emergence of arboviruses. For instance, emergence of a Venezuelan equine encephalitis virus genotype that caused an equine outbreak in Mexico in the 1990s was associated with a single amino-acid substitution in the envelope glycoprotein, which increased infectiousness to the mosquito vector *Ochlerotatus taeniorhynchus* [19]. In this opinion piece, I argue that adaptation to domestic vector species was typically not required for initial emergence of the most medically significant mosquito-borne viruses, although it often occurred secondarily during prolonged virus circulation in the human transmission cycle.

What is the evidence for arbovirus adaptation to domestic mosquitoes?

Yellow fever virus is a mosquito-borne flavivirus causing a hemorrhagic fever with a case-fatality rate up to 50%. It was responsible for devastating disease outbreaks in port cities around the world from the 17th to the early 20th century [20]. Despite an effective vaccine developed in the 1930s, yellow fever virus still represents a significant public health threat because it has been increasingly re-emerging in the last few decades [20,21]. Yellow fever virus is maintained in a enzootic transmission cycle between non-human primates and sylvatic mosquitoes in jungles of Africa and South America [22]. The virus causes sporadic outbreaks when it is introduced into the human population, sometimes via an intermediate transmission cycle that bridges the sylvatic and human transmission cycles [22]. Sustained transmission of yellow fever virus in the human population is typically mediated by the domestic mosquito *Ae. aegypti*, whereas sylvatic transmission involves various mosquito species from the genus *Aedes* in Africa and from the genera *Haemagogus* and *Sabethes* in South America [7]. Although a formal investigation remains to be conducted, there is no indication in the current literature that emergence of yellow fever virus in humans was associated with adaptation for transmission by *Ae. aegypti* [23]. For example, two Brazilian strains of yellow fever virus, one isolated from a human and one isolated from a monkey, were experimentally transmitted at similar rates by Brazilian *Ae. aegypti*, *Haemagogus leucocelaenus* and *Sabethes albiprivus* [24]. The difficulty to rear the sylvatic vectors of yellow fever virus in the laboratory has been a major limitation to carry out such studies.

Dengue viruses also belong to the *Flavivirus* genus and are the most prevalent mosquito-borne viruses of humans – they cause disease in hundreds of millions of people each year

[25]. Four genetic types of dengue viruses evolved from sylvatic progenitors in the last hundreds of years and now circulate endemically in the human population throughout the tropics and sub-tropics [26,27]. Their worldwide emergence since the 18th century has been linked to the geographical expansion of their main mosquito vector, *Ae. aegypti* [28]. Initial dengue virus emergence in the human population required vector switching from arboreal mosquito species, such as *Aedes niveus* in Southeast Asia [8], to the domestic species *Ae. aegypti* and, to a lesser extent, *Ae. albopictus* [29]. Whether this original vector switching was associated with adaptive evolution has been debated but no conclusive evidence has been provided so far. One experimental study based on artificial blood meals found that three sylvatic dengue virus strains were less infectious to contemporaneous *Ae. aegypti* and *Ae. albopictus* mosquitoes than two human strains, supporting the idea that the latter were more adapted for transmission by domestic vectors [30]. However this result was not confirmed when an expanded repertoire of virus strains was included [15], and subsequent studies did not support the hypothesis that dengue virus emergence in humans from sylvatic progenitors required adaptation to domestic vectors [31,32]. Likewise, surrogate human models did not provide any evidence that ancestral sylvatic strains may have required adaptation to replicate more efficiently in humans [33]. Together, these experimental results are consistent with the lack of phylogenetic signature of host-specific adaptations between sylvatic and human strains [26]. On the other hand, dengue virus adaptation for enhanced transmission by *Ae. aegypti* is thought to have occurred continuously after the human transmission cycle was established. Indeed, a large body of literature supports the idea that vector-mediated selection plays a role in dengue virus lineage turnover and clade replacements [34-41]. Enhanced transmission of dengue virus by *Ae. albopictus* was also observed after 10 passages of experimental evolution *in vivo* [42]. This is in line with other studies showing that artificially bypassing one host increases arbovirus fitness in the other host [15].

West Nile virus is a flavivirus transmitted by *Culex* mosquitoes, which was responsible of one of the best studied arboviral emergence events after its 1999 introduction in New York and subsequent spread across North America. West Nile virus primarily infects avian hosts but it can cause disease in humans, who are dead-end hosts because they do not support onwards transmission. With the exception of one positively selected mutation encoding increased viremia in American crows [43], very little adaptive evolution has been observed during West Nile virus emergence in North America [44]. Evidence consistent with adaptation to human-biting mosquitoes was reported in two studies that found more rapid transmission of a newly arising West Nile virus lineage, which had displaced the ancestral lineage originally introduced in New York in 1999 [45,46]. These two studies found that the new lineage had a shorter extrinsic incubation period in *Culex pipiens* and *Culex tarsalis* mosquitoes, however this result

was not confirmed by another study in *Cx. tarsalis* [47]. Evidence for adaptive evolution was also reported in a more recent lineage that showed increased transmissibility and increased prevalence in New York state [48]. Overall, the rapid establishment and spread of West Nile virus following its introduction into the New World is more consistent with 'pre-adaptation' to North American vectors [15].

Chikungunya virus is an alphavirus that caused millions of cases of severe and often chronic arthralgia during human outbreaks in the last two decades. Chikungunya virus originates from Africa where it is maintained in a enzootic cycle involving several species of arboreal mosquito vectors and diverse non-human primates and possibly other vertebrate hosts [49]. The best documented chikungunya emergence events occurred in 2005-2006 on islands of the Indian Ocean and in 2014-2015 after introduction of the virus into the Americas [50]. Disease outbreaks resulted from the establishment of a human transmission cycle involving *Ae. aegypti* and sometimes *Ae. albopictus* [49]. The Indian Ocean outbreaks were associated with the rise of a single mutation in the envelope glycoprotein of the virus (E1-A226V) that enhances transmission by *Ae. albopictus*, but not by *Ae. aegypti* [51,52]. The E1-A226V substitution confers a clear selective advantage in places where *Ae. albopictus* is the predominant vector species. The emergence of this mutation was replicated under laboratory conditions [53] and has become a textbook example of arbovirus adaptation to an alternative mosquito vector species. However, the adaptive nature of the E1-A226V substitution is constrained by epistatic interactions that depend on the viral genetic background [54,55]. There is also ample evidence that chikungunya virus emergence in the human population did not require this mutation or adaptive evolution in general. Chikungunya virus was first discovered in present-day Tanzania during a human outbreak in 1952 [56,57] and subsequently detected in Asia in 1958 during a human outbreak in Thailand [58]. In fact, chikungunya virus may have emerged in Asia as early as the 18th century [59]. Although E1-A226V was selected convergently on at least four separate occasions during the Indian Ocean outbreaks, this adaptive substitution was not responsible for the initial emergence because it is absent from early outbreak isolates [60]. In addition, the chikungunya virus strain that was introduced into the Caribbean in 2013 lacked the E1-A226V mutation, and this mutation has not been detected during the subsequent epidemic spread in the Americas.

Zika virus is a mosquito-borne flavivirus that was first isolated from a sentinel monkey in Uganda in 1947 [61]. During 60 years after its discovery, it was only associated with less than 20 documented human cases and considered innocuous. The first recorded human epidemic of Zika virus occurred in Yap, Micronesia in 2007, where *Aedes hensilli* is thought to have been the main vector [62]. Zika virus subsequently spread to other islands of the South Pacific and

was introduced into Latin America in 2015 [63]. The massive epidemic that followed revealed the ability of Zika virus to cause congenital defects and neurological complications and led the World Health Organization to consider Zika virus a public health emergency of international concern. Zika virus is maintained in an enzootic transmission cycle between non-human primates and arboreal *Aedes* species, whereas transmission in the human cycle is primarily mediated by *Ae. aegypti* [64-66]. The role of adaptive evolution during the spread of Zika virus from the Asia-Pacific region to the Americas has been much debated [67-70]. Reverse genetics studies identified at least four genetic substitutions that preceded Zika virus spread into the South Pacific and the Americas and increased transmission by *Ae. aegypti* [71,72]. However, all four of these substitutions correspond to reversions that restored viral fitness after previous fixation of transmission-reducing mutations, possibly due to founder effects [71,73]. In other words, ancestral Zika virus strains did possess the nucleotide variants associated with high transmissibility by *Ae. aegypti* and were thus 'pre-adapted' for transmission in the human cycle. In fact, contemporaneous Zika virus strains currently circulating in the sylvatic cycle are more transmissible than epidemic strains that were isolated during the recent outbreaks [74].

Conclusions

Retrospective examination of the best studied mosquito-borne arboviruses that have emerged or re-emerged in the last few decades (yellow fever, dengue, West Nile, chikungunya and Zika viruses) indicates that adaptation to domestic mosquito species that act as epidemic vectors likely does not represent a major barrier to initial arbovirus emergence. On several occasions, arbovirus adaptation to domestic mosquitoes contributed to amplify outbreaks but it was not responsible for the initial vector switching. The available evidence is consistent with the idea that emerging mosquito-borne arboviruses are generally 'pre-adapted' to transmission by domestic mosquito vectors. Once the epidemic transmission cycle is established, prolonged circulation in the human population provides increased opportunities for the arbovirus to acquire mutations that further optimize transmission by domestic mosquitoes (Figure 1). This is because the relative strength of natural selection and genetic drift depends on the population size [75]. In small populations, stochastic sampling of variants counteracts selection and hinders adaptation, whereas in larger populations, competition between virus variants occurs with little interference of random processes. Such secondary adaptation for human transmission during large-scale epidemic amplification was observed for Ebola virus [1] and SARS-CoV-2 [2]. Secondary adaptation after pathogen emergence is epidemiologically meaningful and its importance for public health should not be minimized. However, the lack of major constraint to cross the species barrier between enzootic and epidemic mosquito vectors means that initial arbovirus emergence and maintenance depend primarily on ecological rather

than evolutionary processes. Considering that an evolutionary mechanism is not a prerequisite to arbovirus emergence emphasizes the value of risk assessment studies based on the survey and characterization of arboviruses that are naturally circulating in enzootic transmission cycles. Thus, studies on the physiological competence of hosts and vectors, as well as their ecological interactions [76], should provide a relevant assessment of the risk of arbovirus emergence in the human population.

Conflict of interest statement

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the French Government's Investissement d'Avenir program Laboratoire d'Excellence Integrative Biology of Emerging Infectious Diseases (grant ANR-10-LABX-62-IBEID) and MSDAVENIR (grant INTRANZIGEANT). The funding organizations were not involved in the writing or the decision to submit the article for publication.

References and recommended reading

Papers of particular interest, published within the period of the review, have been highlighted as:

* of special interest

** of outstanding interest

1. Urbanowicz RA, McClure CP, Sakuntabhai A, Sall AA, Kobinger G, Muller MA, Holmes EC, Rey FA, Simon-Loriere E, Ball JK: **Human Adaptation of Ebola Virus during the West African Outbreak.** *Cell* 2016, **167**:1079-1087 e1075.
2. Peacock TP, Penrice-Randal R, Hiscox JA, Barclay WS: **SARS-CoV-2 one year on: evidence for ongoing viral adaptation.** *J Gen Virol* 2021, **102**.
3. van Dorp L, Richard D, Tan CCS, Shaw LP, Acman M, Balloux F: **No evidence for increased transmissibility from recurrent mutations in SARS-CoV-2.** *Nat Commun* 2020, **11**:5986.

4. MacLean OA, Lytras S, Weaver S, Singer JB, Boni MF, Lemey P, Kosakovsky Pond SL, Robertson DL: **Natural selection in the evolution of SARS-CoV-2 in bats created a generalist virus and highly capable human pathogen.** *PLoS Biol* 2021, **19**:e3001115.
5. Temmam S, Vongphayloth K, Baquero E, Munier S, Bonomi M, Regnault B, Douangboubpha B, Karami Y, Chretien D, Sanamxay D, et al.: **Bat coronaviruses related to SARS-CoV-2 and infectious for human cells.** *Nature* 2022, **604**:330-336.
6. Warren CJ, Yu S, Peters DK, Barbachano-Guerrero A, Yang Q, Burris BL, Worwa G, Huang IC, Wilkerson GK, Goldberg TL, et al.: **Primate hemorrhagic fever-causing arteriviruses are poised for spillover to humans.** *Cell* 2022, **185**:3980-3991 e3918.
7. Hanley KA, Monath TP, Weaver SC, Rossi SL, Richman RL, Vasilakis N: **Fever versus fever: the role of host and vector susceptibility and interspecific competition in shaping the current and future distributions of the sylvatic cycles of dengue virus and yellow fever virus.** *Infect Genet Evol* 2013, **19**:292-311.
8. Vasilakis N, Cardoso J, Hanley KA, Holmes EC, Weaver SC: **Fever from the forest: prospects for the continued emergence of sylvatic dengue virus and its impact on public health.** *Nat Rev Microbiol* 2011, **9**:532-541.
9. Weaver SC, Charlier C, Vasilakis N, Lecuit M: **Zika, Chikungunya, and Other Emerging Vector-Borne Viral Diseases.** *Annu Rev Med* 2018, **69**:395-408.
10. Kraemer MUG, Reiner RC, Jr., Brady OJ, Messina JP, Gilbert M, Pigott DM, Yi D, Johnson K, Earl L, Marczak LB, et al.: **Past and future spread of the arbovirus vectors *Aedes aegypti* and *Aedes albopictus*.** *Nat Microbiol* 2019, **4**:854-863.
11. Fonseca DM, Keyghobadi N, Malcolm CA, Mehmet C, Schaffner F, Mogi M, Fleischer RC, Wilkerson RC: **Emerging vectors in the *Culex pipiens* complex.** *Science* 2004, **303**:1535-1538.
12. Kilpatrick AM, Kramer LD, Jones MJ, Marra PP, Daszak P: **West Nile virus epidemics in North America are driven by shifts in mosquito feeding behavior.** *PLoS Biol* 2006, **4**:e82.
13. Miot EF, Calvez E, Aubry F, Dabo S, Grandadam M, Marcombe S, Oke C, Logan JG, Brey PT, Lambrechts L: **Risk of arbovirus emergence via bridge vectors: case study of the sylvatic mosquito *Aedes malayensis* in the Nakai district, Laos.** *Sci Rep* 2020, **10**:7750.
14. Pereira Dos Santos T, Roiz D, Santos de Abreu FV, Luz SLB, Santalucia M, Jiolle D, Santos Neves MSA, Simard F, Lourenco-de-Oliveira R, Paupy C: **Potential of *Aedes albopictus* as a bridge vector for enzootic pathogens at the urban-forest interface in Brazil.** *Emerg Microbes Infect* 2018, **7**:191.

15. Coffey LL, Forrester N, Tsetsarkin K, Vasilakis N, Weaver SC: **Factors shaping the adaptive landscape for arboviruses: implications for the emergence of disease.** *Future Microbiol* 2013, **8**:155-176.
 16. Coffey LL, Vasilakis N, Brault AC, Powers AM, Tripet F, Weaver SC: **Arbovirus evolution in vivo is constrained by host alternation.** *Proc Natl Acad Sci U S A* 2008, **105**:6970-6975.
 17. Ruckert C, Ebel GD: **How Do Virus-Mosquito Interactions Lead to Viral Emergence?** *Trends Parasitol* 2018, **34**:310-321.
 18. Yu X, Cheng G: **Adaptive Evolution as a Driving Force of the Emergence and Re-Emergence of Mosquito-Borne Viral Diseases.** *Viruses* 2022, **14**.
 19. Brault AC, Powers AM, Ortiz D, Estrada-Franco JG, Navarro-Lopez R, Weaver SC: **Venezuelan equine encephalitis emergence: enhanced vector infection from a single amino acid substitution in the envelope glycoprotein.** *Proc Natl Acad Sci U S A* 2004, **101**:11344-11349.
- * This study demonstrated that a single mutation of Venezuelan equine encephalitis virus altered its vector host range and likely contributed to its epizootic emergence.
20. Barrett AD, Higgs S: **Yellow fever: a disease that has yet to be conquered.** *Annu Rev Entomol* 2007, **52**:209-229.
 21. Barrett AD: **The reemergence of yellow fever.** *Science* 2018, **361**:847-848.
 22. Barrett AD, Monath TP: **Epidemiology and ecology of yellow fever virus.** *Adv Virus Res* 2003, **61**:291-315.
 23. Shinde DP, Plante JA, Plante KS, Weaver SC: **Yellow Fever: Roles of Animal Models and Arthropod Vector Studies in Understanding Epidemic Emergence.** *Microorganisms* 2022, **10**.
 24. Couto-Lima D, Madec Y, Bersot MI, Campos SS, Motta MA, Santos FBD, Vazeille M, Vasconcelos P, Lourenco-de-Oliveira R, Failloux AB: **Potential risk of re-emergence of urban transmission of Yellow Fever virus in Brazil facilitated by competent Aedes populations.** *Sci Rep* 2017, **7**:4848.
 25. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, Drake JM, Brownstein JS, Hoen AG, Sankoh O, et al.: **The global distribution and burden of dengue.** *Nature* 2013, **496**:504-507.
 26. Holmes EC, Twiddy SS: **The origin, emergence and evolutionary genetics of dengue virus.** *Infect Genet Evol* 2003, **3**:19-28.
- * This study analyzed positive selection among human and sylvatic strains of dengue virus type 2 and did not find phylogenetic evidence for host-specific adaptations.
27. Vasilakis N, Weaver SC: **The history and evolution of human dengue emergence.** *Adv Virus Res* 2008, **72**:1-76.

28. Brady OJ, Hay SI: **The Global Expansion of Dengue: How *Aedes aegypti* Mosquitoes Enabled the First Pandemic Arbovirus.** *Annu Rev Entomol* 2020;191-208.
29. Lambrechts L, Scott TW, Gubler DJ: **Consequences of the expanding global distribution of *Aedes albopictus* for dengue virus transmission.** *PLoS Negl Trop Dis* 2010, **4**:e646.
30. Moncayo AC, Fernandez Z, Ortiz D, Diallo M, Sall A, Hartman S, Davis CT, Coffey L, Mathiot CC, Tesh RB, et al.: **Dengue emergence and adaptation to peridomestic mosquitoes.** *Emerg Infect Dis* 2004, **10**:1790-1796.
31. Diallo M, Ba Y, Faye O, Soumare ML, Dia I, Sall AA: **Vector competence of *Aedes aegypti* populations from Senegal for sylvatic and epidemic dengue 2 virus isolated in West Africa.** *Trans R Soc Trop Med Hyg* 2008, **102**:493-498.
32. Diallo M, Sall AA, Moncayo AC, Ba Y, Fernandez Z, Ortiz D, Coffey LL, Mathiot C, Tesh RB, Weaver SC: **Potential role of sylvatic and domestic African mosquito species in dengue emergence.** *Am J Trop Med Hyg* 2005, **73**:445-449.
33. Vasilakis N, Shell EJ, Fokam EB, Mason PW, Hanley KA, Estes DM, Weaver SC: **Potential of ancestral sylvatic dengue-2 viruses to re-emerge.** *Virology* 2007, **358**:402-412.
34. Anderson JR, Rico-Hesse R: ***Aedes aegypti* vectorial capacity is determined by the infecting genotype of dengue virus.** *Am J Trop Med Hyg* 2006, **75**:886-892.
35. Armstrong PM, Rico-Hesse R: **Differential susceptibility of *Aedes aegypti* to infection by the American and Southeast Asian genotypes of dengue type 2 virus.** *Vector Borne Zoonotic Dis* 2001, **1**:159-168.
36. Armstrong PM, Rico-Hesse R: **Efficiency of dengue serotype 2 virus strains to infect and disseminate in *Aedes aegypti*.** *Am J Trop Med Hyg* 2003, **68**:539-544.
37. Cologna R, Armstrong PM, Rico-Hesse R: **Selection for virulent dengue viruses occurs in humans and mosquitoes.** *J Virol* 2005, **79**:853-859.
38. Hanley KA, Nelson JT, Schirtzinger EE, Whitehead SS, Hanson CT: **Superior infectivity for mosquito vectors contributes to competitive displacement among strains of dengue virus.** *BMC Ecol* 2008, **8**:1.
39. Lambrechts L, Fansiri T, Pongsiri A, Thaisomboonsuk B, Klungthong C, Richardson JH, Ponlawat A, Jarman RG, Scott TW: **Dengue-1 virus clade replacement in Thailand associated with enhanced mosquito transmission.** *J Virol* 2012, **86**:1853-1861.
40. O'Connor O, Ou TP, Aubry F, Dabo S, Russet S, Girault D, In S, Minier M, Lequime S, Hoem T, et al.: **Potential role of vector-mediated natural selection in dengue virus genotype/lineage replacements in two epidemiologically contrasted settings.** *Emerg Microbes Infect* 2021, **10**:1346-1357.
41. Quiner CA, Parameswaran P, Ciota AT, Ehrbar DJ, Dodson BL, Schlesinger S, Kramer LD, Harris E: **Increased replicative fitness of a dengue virus 2 clade in native**

- mosquitoes: potential contribution to a clade replacement event in Nicaragua.** *J Virol* 2014, **88**:13125-13134.
42. Bellone R, Lequime S, Jupille H, Goertz GP, Aubry F, Mousson L, Piorkowski G, Yen PS, Gabiane G, Vazeille M, et al.: **Experimental adaptation of dengue virus 1 to *Aedes albopictus* mosquitoes by in vivo selection.** *Sci Rep* 2020, **10**:18404.
43. Brault AC, Huang CY, Langevin SA, Kinney RM, Bowen RA, Ramey WN, Panella NA, Holmes EC, Powers AM, Miller BR: **A single positively selected West Nile viral mutation confers increased virogenesis in American crows.** *Nat Genet* 2007, **39**:1162-1166.
44. May FJ, Davis CT, Tesh RB, Barrett AD: **Phylogeography of West Nile virus: from the cradle of evolution in Africa to Eurasia, Australia, and the Americas.** *J Virol* 2011, **85**:2964-2974.
45. Ebel GD, Carricaburu J, Young D, Bernard KA, Kramer LD: **Genetic and phenotypic variation of West Nile virus in New York, 2000-2003.** *Am J Trop Med Hyg* 2004, **71**:493-500.
46. Moudy RM, Meola MA, Morin LL, Ebel GD, Kramer LD: **A newly emergent genotype of West Nile virus is transmitted earlier and more efficiently by *Culex* mosquitoes.** *Am J Trop Med Hyg* 2007, **77**:365-370.
47. Anderson JF, Main AJ, Cheng G, Ferrandino FJ, Fikrig E: **Horizontal and vertical transmission of West Nile virus genotype NY99 by *Culex salinarius* and genotypes NY99 and WN02 by *Culex tarsalis*.** *Am J Trop Med Hyg* 2012, **86**:134-139.
48. Bialosuknia SM, Dupuis li AP, Zink SD, Koetzner CA, Maffei JG, Owen JC, Landwerlen H, Kramer LD, Ciota AT: **Adaptive evolution of West Nile virus facilitated increased transmissibility and prevalence in New York State.** *Emerg Microbes Infect* 2022, **11**:988-999.
49. Weaver SC, Chen R, Diallo M: **Chikungunya Virus: Role of Vectors in Emergence from Enzootic Cycles.** *Annu Rev Entomol* 2020, **65**:313-332.
50. Weaver SC, Lecuit M: **Chikungunya virus and the global spread of a mosquito-borne disease.** *N Engl J Med* 2015, **372**:1231-1239.
51. Tsetsarkin KA, Vanlandingham DL, McGee CE, Higgs S: **A Single Mutation in Chikungunya Virus Affects Vector Specificity and Epidemic Potential.** *PLoS Pathog* 2007, **3**:e201.
- ** This study demonstrated that a single mutation of chikungunya virus enhanced its infectiousness to an ancillary mosquito vector, providing an explanation to a large-scale outbreak that occurred in a region lacking the typical vector.

52. Vazeille M, Moutailler S, Coudrier D, Rousseaux C, Khun H, Huerre M, Thiria J, Dehecq JS, Fontenille D, Schuffenecker I, et al.: **Two Chikungunya isolates from the outbreak of La Reunion (Indian Ocean) exhibit different patterns of infection in the mosquito, *Aedes albopictus***. *PLoS ONE* 2007, **2**:e1168.
53. Stapleford KA, Coffey LL, Lay S, Borderia AV, Duong V, Isakov O, Rozen-Gagnon K, Arias-Goeta C, Blanc H, Beaucourt S, et al.: **Emergence and transmission of arbovirus evolutionary intermediates with epidemic potential**. *Cell Host Microbe* 2014, **15**:706-716.
- ** This study experimentally recapitulated the adaptive evolution of a chikungunya virus mutation that confers enhanced transmission.
54. Chen R, Plante JA, Plante KS, Yun R, Shinde D, Liu J, Haller S, Mukhopadhyay S, Weaver SC: **Lineage Divergence and Vector-Specific Adaptation Have Driven Chikungunya Virus onto Multiple Adaptive Landscapes**. *mBio* 2021, **12**:e0273821.
55. Tsetsarkin KA, Chen R, Leal G, Forrester N, Higgs S, Huang J, Weaver SC: **Chikungunya virus emergence is constrained in Asia by lineage-specific adaptive landscapes**. *Proc Natl Acad Sci U S A* 2011, **108**:7872-7877.
- * This study demonstrated that the effect of a transmission-adaptive mutation of chikungunya virus is conditioned by the viral genetic background through epistatic interactions.
56. Lumsden WH: **An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952-53. II. General description and epidemiology**. *Trans R Soc Trop Med Hyg* 1955, **49**:33-57.
57. Ross RW: **The Newala epidemic. III. The virus: isolation, pathogenic properties and relationship to the epidemic**. *J Hyg (Lond)* 1956, **54**:177-191.
58. Hammon WM, Rudnick A, Sather GE: **Viruses associated with epidemic hemorrhagic fevers of the Philippines and Thailand**. *Science* 1960, **131**:1102-1103.
59. Weaver SC, Forrester NL: **Chikungunya: Evolutionary history and recent epidemic spread**. *Antiviral Res* 2015, **120**:32-39.
60. Tsetsarkin KA, Chen R, Sherman MB, Weaver SC: **Chikungunya virus: evolution and genetic determinants of emergence**. *Curr Opin Virol* 2011, **1**:310-317.
61. Dick GW, Kitchen SF, Haddock AJ: **Zika virus. I. Isolations and serological specificity**. *Trans R Soc Trop Med Hyg* 1952, **46**:509-520.
62. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, Pretrick M, Marfel M, Holzbauer S, Dubray C, et al.: **Zika virus outbreak on Yap Island, Federated States of Micronesia**. *N Engl J Med* 2009, **360**:2536-2543.
63. Musso D, Ko AI, Baud D: **Zika Virus Infection - After the Pandemic**. *N Engl J Med* 2019, **381**:1444-1457.

64. Gutierrez-Bugallo G, Piedra LA, Rodriguez M, Bisset JA, Lourenco-de-Oliveira R, Weaver SC, Vasilakis N, Vega-Rua A: **Vector-borne transmission and evolution of Zika virus.** *Nat Ecol Evol* 2019, **3**:561-569.
65. Obadia T, Gutierrez-Bugallo G, Duong V, Nunez AI, Fernandes RS, Kamgang B, Hery L, Gomard Y, Abbo SR, Jiolle D, et al.: **Zika vector competence data reveals risks of outbreaks: the contribution of the European ZIKAlliance project.** *Nat Commun* 2022, **13**:4490.
66. Petersen LR, Jamieson DJ, Powers AM, Honein MA: **Zika Virus.** *N Engl J Med* 2016, **374**:1552-1563.
67. Liu ZY, Shi WF, Qin CF: **The evolution of Zika virus from Asia to the Americas.** *Nat Rev Microbiol* 2019, **17**:131-139.
68. Pettersson JH, Eldholm V, Seligman SJ, Lundkvist A, Falconar AK, Gaunt MW, Musso D, Nougairede A, Charrel R, Gould EA, et al.: **How Did Zika Virus Emerge in the Pacific Islands and Latin America?** *mBio* 2016, **7**.
69. Rossi SL, Ebel GD, Shan C, Shi PY, Vasilakis N: **Did Zika Virus Mutate to Cause Severe Outbreaks?** *Trends Microbiol* 2018, **26**:877-885.
70. Weaver SC: **Emergence of Epidemic Zika Virus Transmission and Congenital Zika Syndrome: Are Recently Evolved Traits to Blame?** *mBio* 2017, **8**.
71. Liu J, Liu Y, Shan C, Nunes BT, Yun R, Haller SL, Rafael GH, Azar SR, Andersen CR, Plante K, et al.: **Role of mutational reversions and fitness restoration in Zika virus spread to the Americas.** *Nat Commun* 2021, **12**:595.
- * This study demonstrated that several mutations that occurred prior the geographical expansion of Zika virus were direct reversions of previous mutations that had reduced epidemic fitness relative to the ancestral sylvatic strains.
72. Liu Y, Liu J, Du S, Shan C, Nie K, Zhang R, Li XF, Zhang R, Wang T, Qin CF, et al.: **Evolutionary enhancement of Zika virus infectivity in *Aedes aegypti* mosquitoes.** *Nature* 2017, **545**:482-486.
73. Weaver SC, Forrester NL, Liu J, Vasilakis N: **Population bottlenecks and founder effects: implications for mosquito-borne arboviral emergence.** *Nat Rev Microbiol* 2021, **19**:184-195.
74. Aubry F, Jacobs S, Darmuzey M, Lequime S, Delang L, Fontaine A, Jupatanakul N, Miot EF, Dabo S, Manet C, et al.: **Recent African strains of Zika virus display higher transmissibility and fetal pathogenicity than Asian strains.** *Nat Commun* 2021, **12**:916.
- ** This study provided unequivocal evidence that Zika virus strains circulating in the sylvatic transmission cycle are more transmissible by domestic vectors than epidemic strains.
75. Wright S: **Evolution in Mendelian Populations.** *Genetics* 1931, **16**:97-159.

76. Kain MP, Skinner EB, van den Hurk AF, McCallum H, Mordecai EA: **Physiology and ecology combine to determine host and vector importance for Ross River virus.** *Elife* 2021, **10**.

Figure

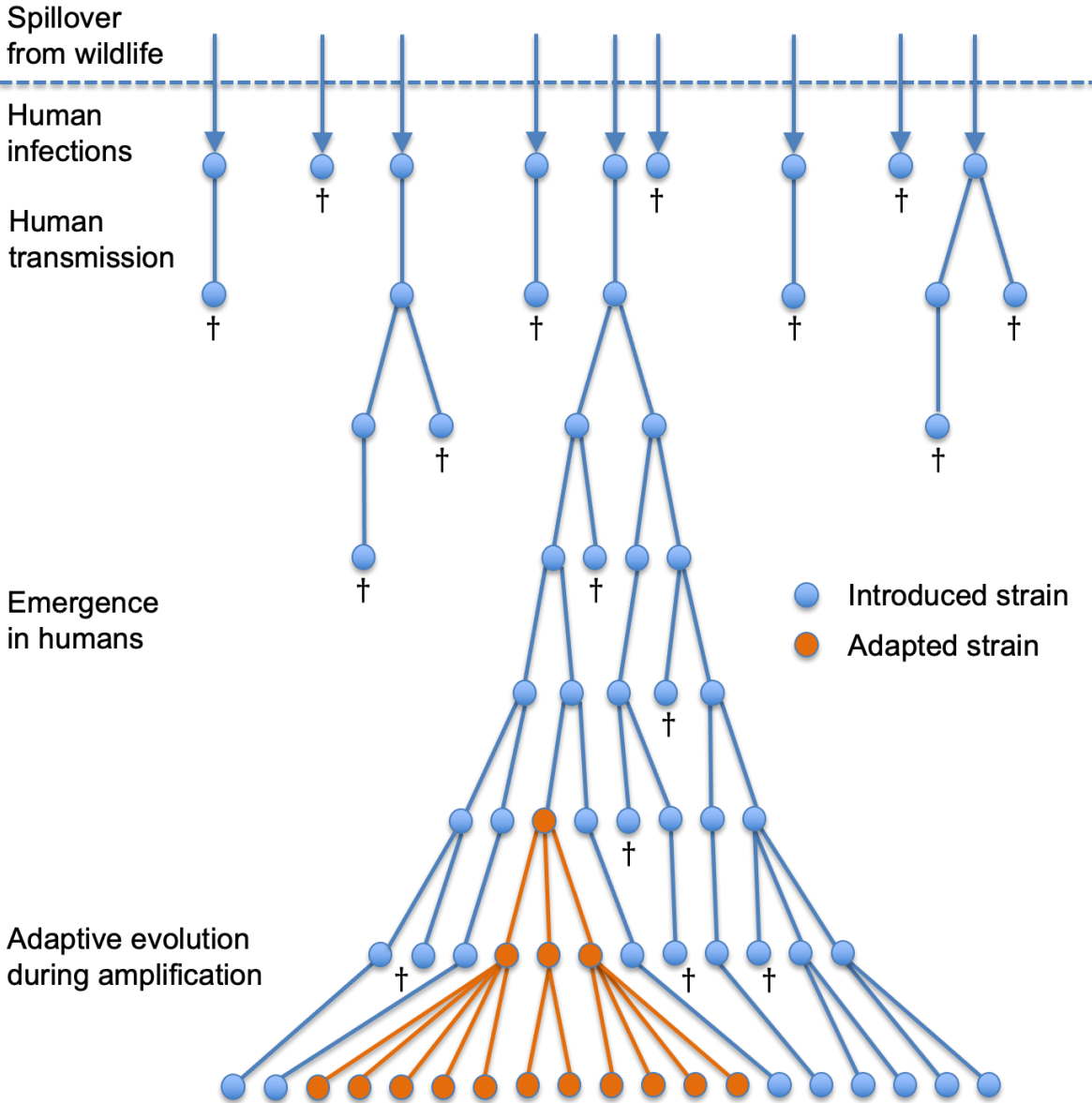


Figure 1. Schematic for the emergence of a zoonotic pathogen with secondary adaptation for human transmission during epidemic amplification. Introductions from the zoonotic transmission cycle are followed by chains of transmission in the human population. Dagggers indicate no further transmission. Blue circles represent human infections with the introduced strain whereas orange circles represent infections with an evolved strain that is more adapted for human transmission. Adaptive evolution is more likely to occur during epidemic amplification of the introduced strain because of the larger population size.